UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,640	12/15/2003	Bruno de Lignieres	088734-1111	9061

22428 7590 08/04/2009
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
08/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,640	LIGNIERES ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4, 5-14 are currently pending and are being examined on the merits herein.

Response to Remarks/Arguments

Applicants' arguments regarding the 103(a) rejections have been fully considered but are not found to be persuasive. Further search and consideration necessitated the new rejections presented in this office action. Accordingly, the action is made non-final.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-10, 12, 13 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No.

7,507,769 in view of Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284).

The claims of the instant application teach a method of treating mastalgia comprising administering 4-OH tamoxifen percutaneously to the breasts of a patient (1.5 – 2.0 mg/day)

The claims of the patent '769 teaches a method of treatment, comprising percutaneously administering an effective amount of 4-hydroxy tamoxifen to a female patient having benign breast disease, wherein said 4-hydroxy tamoxifen and wherein said benign breast disease is selected from the group consisting of adenosis, cysts, duct ectasia, fibroadenoma, fibrocystic disease, fibrosis, hyperplasia and metaplasia and wherein said vehicle is a hydroalcoholic gel or hydroalcoholic solution comprising 4-hydroxy tamoxifen, isopropyl myristate, absolute alcohol and a gelling agent.

The patent does not teach the benign breast disease as mastalgia as claimed.

Jarvis (Current Therapy in Endocrinology and Metabolism) studies teaches breast pain (mastodynia or mastalgia) as one of the symptoms of benign breast disease and further teach that studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease (p 281, col. 1, col. 2, Antiestrogens).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the patent teach a method of

treating a benign breast condition administering a hydoalcoholic gel comprising 4-OH tamoxifen. It would have been obvious to one having ordinary skill in the art at the time of the invention to have used 4-OH tamoxifen in a method of treating mastalgia because Jarvis teaches breast pain (mastodynia or mastalgia) as one of the symptoms of benign breast disease and further teach that studies have been performed to determine if 4-hydroxy tamoxifen can be used to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease.

Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 18 of copending Application No. 11/249,122.

The claims of the instant application teach a method of treating mastalgia comprising administering 4-OH tamoxifen percutaneously to the breasts of a patient (1.5 – 2.0 mg/day)

The co-pending application teaches a method of treating a breast condition including mastalgia, keloid, gynecomastia, breast cancer etc. comprising administering a hydoalcoholic gel comprising 4-OH tamoxifen.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and the co-pending application teach a method of treating mastalgia administering a hydoalcoholic gel comprising 4-OH tamoxifen.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 6-8, 10, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al. (Applicant cited IDS: U.S. 4,919,937) and Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Jarvis et al. teaches a method of treating conditions of the breast including the steps of: forming an aqueous alcoholic gel in which the active ingredient consists of 4-

OH tamoxifen and administering percutaneously said aqueous alcoholic gel as an anti-estrogen drug to a breast (col. 4, claim 1). Jarvis et al. teaches that the daily doses of product to be administered are easy to calculate in terms of the absorption coefficients of the drugs and the doses which it is desired to obtain for 4-hydroxytamoxifen at the level of the receptor molecule (col.3, lines 23-28, see claims). The reference teaches that the drug 4-OH tamoxifen finds application in the treatment of conditions of the breast, especially benign and even cancerous conditions of the breast (col. 4, lines 37-39).

Jarvis (Current Therapy in Endocrinology and Metabolism) studies teaches breast pain (mastodynia or mastalgia) as one of the symptoms of benign breast disease and further teach that studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease (p 281, col. 1, col. 2, Antiestrogens).

The references do not teach the amount of 4-hydroxy tamoxifen in the percutaneous administration.

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design).

Jarvis and Pujol et al. do not teach mastalgia to be cyclical.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12). The reference further teaches the agent proved to be significantly more effective in the relief of cyclical rather than non cyclical pain (see abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-hydroxy tamoxifen at a dose of at least 1.5 mg/day or the dosages claimed in the instant invention. One of ordinary skill in the art would have been motivated to administer such claimed amounts of 4-hydroxy tamoxifen in the treatment of mastalgia because of expectation of success as Pujol et al. clearly teaches percutaneous administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). It would have been obvious to one of

ordinary skill in the art to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia. One of ordinary skill in the art would have been motivated to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia in expectation of success because of the teachings of Jarvis and Fentiman. Jarvis teach the use of 4-hydroxy tamoxifen in benign breast disease conditions (mastalgia, which includes both cyclical and non-cyclical is one of the symptoms of benign breast disease) and Fentiman teaches the use of tamoxifen in the treatment of both cyclical and non-cyclical breast pain. Mastalgia is breast pain and is generally classified as either cyclical (associated with menstrual periods) or noncyclic. Jarvis in essence teaches the use of 4-OH tamoxifen in the treatment of breast conditions including benign breast disease and breast pain being one of the symptoms of the breast disease is obviously treated upon administration of 4-OH tamoxifen.

Claims 1-3, 6-8, 10, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al .(Applicant cited IDS: U.S. 4,919,937) and Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Jarvis et al. teaches a method of treating conditions of the breast including the steps of: forming an aqueous alcoholic gel in which the active ingredient consists of 4-OH tamoxifen and administering percutaneously said aqueous alcoholic gel as an anti-estrogen drug to a breast (col. 4, claim 1). Jarvis et al. teaches that the daily doses of

product to be administered are easy to calculate in terms of the absorption coefficients of the drugs and the doses which it is desired to obtain for 4-hydroxytamoxifen at the level of the receptor molecule (col.3, lines 23-28). The reference teaches that the drug 4-OH tamoxifen finds application in the treatment of conditions of the breast, especially benign and even cancerous conditions of the breast (col. 4, lines 37-39).

Jarvis et al. (("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986) studies teaches breast pain (mastodynia or mastalgia) as one of the symptoms of benign breast disease and further teach that studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease (p 129, 130, Therapeutic Alternatives, Antiestrogens).

The references do not teach the amount of 4-hydroxy tamoxifen in the percutaneous administration.

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design).

Jarvis and Pujol et al. do not teach mastalgia to be cyclical.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12). The reference further teaches the

agent proved to be significantly more effective in the relief of cyclical rather than non cyclical pain (see abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-hydroxy tamoxifen at a dose of at least 1.5 mg/day or the dosages claimed in the instant invention. One of ordinary skill in the art would have been motivated to administer such claimed amounts of 4-hydroxy tamoxifen in the treatment of mastalgia because of expectation of success as Pujol et al. clearly teaches percutaneous administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia. One of ordinary skill in the art would have been motivated to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia in expectation of success

because of the teachings of Jarvis and Fentiman. Jarvis teach the use of 4-hydroxy tamoxifen in benign breast disease conditions (mastalgia, which includes both cyclical and non-cyclical is one of the symptoms of benign breast disease) and Fentiman teaches the use of tamoxifen in the treatment of both cyclical and non-cyclical breast pain. Mastalgia is breast pain and is generally classified as either cyclical (associated with menstrual periods) or noncyclic. Jarvis in essence teaches the use of 4-OH tamoxifen in the treatment of breast conditions including benign breast disease and breast pain being one of the symptoms of the breast disease is obviously treated upon administration of 4-OH tamoxifen.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al .(Applicant cited IDS: U.S. 4,919,937) and Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Kochinke et al. (U.S. 5,613,958).

The teachings of Jarvis ('937 patent), Jarvis (Curr Therapy Endocrin and Met), Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

The prior art from Jarvis (both references), Pujol et al. and Fentiman et al. do not teach the hydroalcoholic gel comprising ethanol, isopropyl myristate and hydroxypropyl cellulose.

Kochinke et al. teaches a transdermal drug delivery system comprising a drug, plasticizer-type enhancer such as isopropyl myristate, a solvent-type enhancer such as ethanol and a gelling agent such as hydroxypropyl cellulose (col. 9, lines 23-25, 47-59, col. 11, lines 6-25).

It would have been obvious to one of ordinary skill in the art to use a combination of isopropyl myristate, ethanol, and hydroxypropyl cellulose as a hydroalcoholic gel solution in the percutaneous delivery of 4-OH tamoxifen. The motivation to do so is provided by Kochinke et al. The reference teaches that solvent-type enhancer such as ethanol provide higher flux rate, plasticizer-type enhancer such as isopropyl myristate is used in combination with a solvent-type enhancer to deliver drugs through stratum corneum at therapeutically effective levels and to eliminate the irritation that occurs when solvent-type enhancers are used alone at high concentrations. In addition the reference teaches that a gelling agent such as hydroxypropylcellulose is added to increase the viscosity and rheological characteristics of the drug and enhancers.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al .(Applicant cited IDS: U.S. 4,919,937) and Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Kochinke et al. (U.S. 5,613,958).

The teachings of Jarvis ('937 patent), Jarvis ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris), Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

The prior art from Jarvis (both references), Pujol et al. and Fentiman et al. do not teach the hydroalcoholic gel comprising ethanol, isopropyl myristate and hydroxypropyl cellulose.

Kochinke et al. teaches a transdermal drug delivery system comprising a drug, plasticizer-type enhancer such as isopropyl myristate, a solvent-type enhancer such as ethanol and a gelling agent such as hydroxypropyl cellulose (col. 9, lines 23-25, 47-59, col. 11, lines 6-25).

It would have been obvious to one of ordinary skill in the art to use a combination of isopropyl myristate, ethanol, and hydroxypropyl cellulose as a hydroalcoholic gel solution in the percutaneous delivery of 4-OH tamoxifen. The motivation to do so is provided by Kochinke et al. The reference teaches that solvent-type enhancer such as ethanol provide higher flux rate, plasticizer-type enhancer such as isopropyl myristate is used in combination with a solvent-type enhancer to deliver drugs through stratum corneum at therapeutically effective levels and to eliminate the irritation that occurs when solvent-type enhancers are used alone at high concentrations. In addition the reference teaches that a gelling agent such as hydroxypropylcellulose is added to increase the viscosity and rheological characteristics of the drug and enhancers.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al .(Applicant cited IDS: U.S. 4,919,937) and Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Malet et al (Cancer Research, 48, 7193-7199, 1988).

The teachings of Jarvis ('937 patent), Jarvis (Current Therapy in Endocrinology and Metabolism), Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

Jarvis ('937 patent) teaches the use of mixture of cis and trans isomers of 4-OH tamoxifen in a method of treating benign breast conditions. The reference further teach the separation of the isomers. However, the references discussed above do not explicitly teach the use of trans isomer alone in a method of treating a breast condition such as mastalgia.

Malet teaches percutaneous administration of trans 4-hydroxy tamoxifen to human breast of patients (see Abstract). The reference further teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen and further teaches that cis isomer has estrogenic agonistic effect (p 7193, col.2, para 4, lines 11-12) and the antiproliferative effects are weaker than that of the trans isomer (p 7199, col. 1, lines 4-5).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have administered a trans isomer of 4-OH tamoxifen in the treatment of mastalgia because of the teachings of Malet et al. Malet et al. reference teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen. The reference further teaches that cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect and a percutaneous administration of trans 4-hydroxy tamoxifen could produce a strong antiestrogenic effect at the molecular level. One having ordinary skill in the art would have been motivated to administer the trans isomer of 4-OH tamoxifen in the treatment of mastalgia because cis isomer has antiproliferative effects that are weaker than that of the trans isomer and cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al .(Applicant cited IDS: U.S. 4,919,937) and Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Malet et al (Cancer Research, 48, 7193-7199, 1988).

The teachings of Jarvis ('937 patent), Jarvis ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris), Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

Jarvis ('937 patent) teaches the use of mixture of cis and trans isomers of 4-OH tamoxifen in a method of treating benign breast conditions. The reference further teach the separation of the isomers. However, the references discussed above do not explicitly teach the use of trans isomer alone in a method of treating a breast condition such as mastalgia.

Malet teaches percutaneous administration of trans 4-hydroxy tamoxifen to human breast of patients (see Abstract). The reference further teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen and further teaches that cis isomer has estrogenic agonistic effect (p 7193, col.2, para 4, lines 11-12) and the antiproliferative effects are weaker than that of the trans isomer (p 7199, col. 1, lines 4-5).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have administered a trans isomer of 4-OH tamoxifen in the treatment of mastalgia because of the teachings of Malet et al. Malet et al. reference teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen. The reference further teaches that cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect and a percutaneous administration of trans 4-hydroxy tamoxifen could produce a strong antiestrogenic effect at the molecular level. One having ordinary skill in the art would have been motivated to administer the trans isomer of 4-OH tamoxifen in the treatment of mastalgia because cis isomer has antiproliferative effects that are weaker than that of the trans isomer and cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect.

Response to Arguments/Remarks

Applicants' argue that "the continued reliance on the reported estrogen receptor affinity of 4-OHT to support the obviousness rejections is not supported by the record as whole, and indeed is contrary to the evidence provided in the Hilt Declaration. Moreover, as attested in the Hilt Declaration, neither of the cited Mauvais-Jarvis articles provides any basis on which the person skilled in the art reasonably could predict that 4-OHT could be used to treat mastalgia, as recited in the instant claims. Hilt Declaration, ¶¶ 27, 28". In response, Jarvis patent teaches the administration of 4-OH tamoxifen in treating benign breast conditions and the rejection is not based on substituting 4-OH tamoxifen for tamoxifen. Both Jarvis's art has been cited to show that mastalgia is a benign breast disease and not as an art to show that 4-hydroxy tamoxifen can be used for tamoxifen.

Applicants' argue that Fentiman for teaching the use of oral tamoxifen to treat cyclical or non-cyclical mastalgia. The Hilt Declaration evidences that Fentiman's work with tamoxifen in no way suggests that similar results could be achieved with 4-OHT. Hilt Declaration, ¶¶ 8, 24. Fentiman has been cited to show that mastalgia can be cyclical. As stated above, Jarvis patent teaches the administration of 4-OH tamoxifen in treating benign breast conditions and the rejection is not based on substituting 4-OH tamoxifen for tamoxifen.

Applicants' argue that "The Examiner's failure to take into account the evidence provided in the Hilt Declaration is contrary to MPEP § 2145, which requires Examiners to consider and give appropriate weight to all evidence of non-obviousness". In response, Hilt's declaration has been fully considered and Jarvis patent teaches the

administration of 4-OH tamoxifen in treating benign breast conditions and the rejection is not based on substituting 4-OH tamoxifen for tamoxifen.

Applicants' argue that "Pujol does not teach or suggest application to the breasts of the amounts of 4- OHT recited in the instant claims". Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer. Pujol teaches an amount of 2.0 mg/day and amount of administration is clearly a result effective parameter that can be routinely optimized by varying the amount of administration. Applicant, in fact in claim 7 of the instant application teaches administration of 1.0 mg/day/breast which accounts to 2.0 mg/day of administration. Hence it would have been obvious to one having ordinary skill in the art at the time of the invention to have adjusted the amounts to 1.5 mg/day as claimed. MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955);

Applicants' argue that there is no teaching or suggestion in the cited references that would have led the skilled artisan to combine the teachings of the Mauvais-Jarvis references with Pujol, and then modify the teachings of Pujol to arrive at the claimed invention. In response, Jarvis patent clearly teaches the administration of 4-OH tamoxifen in benign breast conditions and Jarvis (non patent art) teaches mastalgia as one of the benign breast conditions and even suggest treatment of the same with 4-OH tamoxifen. Pujol's teachings have been cited to show the varying amounts of 4-hydroxy

tamoxifen that has been safe in treating breast cancer. Hence the combined references provides a teaching of using 4-OH tamoxifen in benign breast conditions, teaches mastalgia as a benign breast condition and also the amounts that are effective and safe in treating breast conditions.

Applicants' argue that "the Office Actions cites In re Aller in support of the obviousness rejection, but that case does not apply here". In response, it is clear from the teachings of Jarvis patent that 4-OH tamoxifen is beneficial in treating benign breast conditions. Jarvis' other teachings suggest using 4-OH tamoxifen in treating mastalgia, a benign breast condition. Pujol teaches administration of 4-OH tamoxifen in treating breast conditions such as cancer. Hence it would have been obvious to one having ordinary skill in the art from the teachings Pujol that amounts of 0.5 mg, 1.0 mg and 2.0 mg of 4-OH tamoxifen would be a safe dosage to start with. Dosage is clearly a result effective parameter that can be routinely optimized based on the therapeutic effectiveness, medical conditions, age etc. Hence it would have been obvious to one having ordinary skill in the art at the time of the invention to have used 1.5 mg/day or 2.0 mg/day of 4-OH tamoxifen in expectation of obtaining therapeutic benefits in a method of treating a breast condition such as mastalgia.

Applicants; argue that it would have not have been obvious to try 4-OH tamoxifen in the recited methods. As stated above, Jarvis patent teaches the administration of 4-OH tamoxifen in treating benign breast conditions and the rejection is not based on substituting 4-OH tamoxifen for tamoxifen. There is no obvious to try situation presented in the above 103 rejections.

Applicants' argue that combining Malet with the other references, however, still fails to establish a prima facie case of obviousness of the method recited in claim 4 or combining Kochinke with the other references, however, still fails to establish a prima facie case of obviousness of the method recited in claim 9. Jarvis patent teaches the administration of 4-OH tamoxifen in treating benign breast conditions and Jarvis's non patent literature teaches mastalgia as a benign breast disease and further suggest administration of 4-OHT for treating such conditions. Jarvis patent teaches a racemic mixture of 4-OH tamoxifen (cis and trans) and Malet has been cited to show that trans isomer of 4-OHT is known in the art and has stronger antiproliferative effects than the cis isomer. Kochinke is cited for teaching a composition comprising isopropyl myristate, ethanol and hydroxypropylcellulose. The combined references provides a teaching of using 4-OH tamoxifen in benign breast conditions, teaches mastalgia as a benign breast condition and also the amounts that are effective and safe in treating breast conditions.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617